REMARKS

Applicants hereby acknowledge the finality of the Requirement for Restriction and appreciate the Examiner's explanation of the matrix-type description of the requirement. Upon entry of this amendment, the claims under examination are claims 1, 3, 14-25, 27, and 38.

Applicants further acknowledge that the Examiner has not considered that portion of the Information Disclosure Statement for which references were not provided.

Applicants request cancellation of claims 2 and 26 without prejudice and without disclaimer as to the subject matter thereof, as the subject matter of claims 2 and 26 have been incorporated into claim 1. Therefore, the objection to claim 26 is moot. Applicants respectfully submit that the claims are in proper form for allowance.

Claim Amendments

Applicants have amended claims 1 and 14-26 to include the feature that the bacteria are exposed to a plurality of antibiotics. The dependent claims further state which antibiotics are included in the plurality of antibiotics. Support for the amendments may be found, for example in the original claims which state that the bacteria may be exposed to "at least one" antibiotic which may be the antibiotics detailed in the dependent claims.

35 U.S.C. §§ 102(b) and (e)

The Office Action rejects claims 1-3, 15 and 38 under 35 U.S.C. §102(e) as anticipated by Pre-Grant Publication 2002/0068284 to Nicolaides *et al.* ("Nicolaides I"). Nicolaides I does not teach exposing the bacteria to a plurality of antibiotics. Thus, Nicolaides I does not anticipate claims 1-3, and 15.

The Office Action rejects claim 38 under 35 U.S.C. §102(b) over U.S. Patent No. 6,025,400 to Lin ("Lin") or to U.S. Patent No. 6,043,048 to Johnson ("Johnson"). The Office Action further states that the patentability of the product in claim 38 is based on the product itself and not by the process by which it was made (citing *In re Thorpe* 227 U.S.P.Q. 964, 966 (Fed. Cir. 1985)). Applicants have amended claim 38 to include the feature that the multiantibiotic resistant bacteria comprise a dominant negative form of a mismatch repair gene, and added claim 42 which specifies that the dominant negative allele is a *PMS2-134*. Neither Lin nor Johnson teaches or suggests bacteria comprising a dominant negative form of a mismatch repair gene. Thus, neither Lin nor Johnson anticipates claim 38. Moreover, the product presently claimed by claim 38 is novel in that a multiantibiotic resistant bacterium comprising a dominant negative allele of a mismatch repair gene has not been described.

Applicants respectfully request withdrawal of the rejection of claims 1-3, 15 and 38 under 35 U.S.C. §§102(b) and (e).

35 U.S.C. § 103(a)

The Office Action rejects claims 1-3, 15, 27 and 38 as obvious over Nicolaides I as applied in the rejection under 35 U.S.C. §102(e) and in further of the teaching in Nicolaides I of restoring genetic stability in the bacterial cells. The claims, as amended are not obvious in view of Nicolaides I in that Nicolaides I does not teach that bacteria may be exposed to more than one antibiotic simultaneously and multiantibiotic resistant bacteria selected therefrom. There is no inherent teaching in Nicolaides that would give one of skill in the art a reasonable expectation of success in making multiantibiotic resistant bacteria. Thus, the step of restoring genetic stability of such cells is also not

taught by Nicolaides I. Applicants respectfully request withdrawal of the rejection of claims 1-3, 15, 27 and 38 35 U.S.C. §103(a) over Nicolaides I.

The Office Action also rejects claims 1, 19, 27 and 38 under 35 U.S.C. §103(a) over U.S. Patent No. 6,221,585 to Iris *et al.* ("Iris") in view of U.S. Pre-Grant Publication 2002/0049104 to Stemmer *et al.* ("Stemmer") and U.S. Patent No. 6,043,048 to Johnson *et al.* ("Johnson"). The Office Action cites Stemmer for teaching generation of diversity using mismatch repair deficient host strains. The Office Action also cites U.S. Patent No. 6,158,035 to Ashby *et al.* ("Ashby") for providing motivation for generating multiple phenotypes for antibiotic resistance. Johnson is cited for the proposition that it was known in the art to generate resistance to antibiotics by exposing bacteria to the antibiotics. Without conceding the correctness of the Examiner's argument, it is noted that claim 1 has been amended to include the feature of claim 2. That is, that hypermutability of the cells in generated by introducing into the bacteria a dominant negative allele of a mismatch repair gene. The Applicants specifically reserve the right to file continuation or divisional applications drawn to the method that makes use of other means of creating mismatch repair deficiency in the bacterial cells. Iris, Stemmer, Ashby and Johnson all fail to teach the generation of diversity by introducing into cells a dominant negative allele of a mismatch repair gene, as admitted by the Examiner in paragraph 15 of the Office Action. For a *prima facie* case of obviousness, the references must teach or suggest the combination without resort to hindsight construction. As none of these references teaches the use of dominant negative alleles of mismatch repair genes to introduce genetic alterations leading to new phenotypes (such as multiantibiotic resistance) and none of the references, alone or in combination, provide a reasonable

expectation of success that the introduction of dominant negative alleles would promote sufficient diversity in the cells as to create multiantibiotic resistance, the claims are not obvious in view of the references.

Further, the Examiner frankly admits that the restabilization of the genome is not taught by any of the references. Thus, as the method as claimed in the amended claims is not obvious in light of the hypothetical combination of references, the additional step of restabilization is one step more removed from the obviousness analysis, and also cannot be obvious.

Applicants respectfully request withdrawal of the rejection under 35 U.S.C. §103(a) over the hypothetical combination of Iris, Stemmer, Ashby and Johnson.

The Office Action also rejects claims 1, 2, 19, 27 and 38 under 35 U.S.C. §103(a) over Iris in view of Stemmer and Johnson, and further in view of Aronshtam and Marinus (1996) *Nucl. Acids Res.* 24(13):2498-2504 ("Aronshtam"). The Office Action cites Aronshtam for teaching dominant negative alleles of a mismatch repair gene as a means of inhibiting mismatch repair in bacterial cells.

Iris teaches a method of identifying genes associated with a desired phenotype by examining mismatched duplex nucleic acid molecules formed from the hybridization of two source populations (such as two cosanguinous individuals). The mismatched hybridized molecules presumably comprise the polynucleotides responsible for the altered phenotypes. Stemmer describes a method for identifying and controlling genetic and metabolic pathways underlying complex phenotypes through the use of conjoint polynucleotides (*i.e.*, multiple polynucleotide segments joined together in a linear end-to-end array). This method involves piecing together known genetic segments by ligation,

into episomal vectors to produce libraries of the conjoint polynucleotides. The conjoint polynucleotides may be mutated before or after assembly. One method that is mentioned for mutating the polynucleotide portions is to produce the polynucleotides in mismatch repair deficient hosts. Stemmer, however, does not state that such diversity may be achieved by introducing dominant negative alleles of mismatch repair genes into the cells. In the hypothetical combination suggested by the Office Action, it is suggested that the use of mismatch repair defective cells could be used in the method of Iris. However, the method of Iris requires two populations of cells: one that displays the desired phenotype and one that does not. Iris does not teach a method of how to first obtain an antibiotic resistant organism. Stemmer discloses the use of mismatch repair defective host cells to evolve the concatamers of the invention prior to or following selection of the conjoint constructs, not to evolve wild-type gene segments prior to artificially constructing the conjoint gene segments (see page 11, paragraph 0113). Thus, the diversity generating methods mentioned by Stemmer are specifically used to promote diversity of episomes, not whole cells for creating new phenotypes. Aronshtam studied the functional domains of *MutL* and identified mutants that conferred a dominant negative effect on mismatch repair. However, Aronshtam does not teach or suggest using dominant negative alleles of mismatch repair genes to transfect cells to create multiantibiotic resistant bacteria. Although Johnson may teach that it was known in the art to select antibiotic resistant bacteria from cultures of bacteria exposed to antibiotics, there is no motivation to do this in conjunction with Aronshtam and Stemmer. The use of dominant negative mismatch repair alleles in the method of Stemmer to create diversity was for the specific use of increasing the diversity of an episomal construct. Even in

combination with the method Iris, one of skill in the art would not achieve the method of the invention as Iris requires a screening procedure based on hybridization of nucleic acid molecules derived from different sources, and does not teach or suggest screening for multiantibiotic resistance on a phenotypic level by a process of selection, as claimed in the present application. The only motivation of combining these references is impermissible hindsight. The references do not teach or suggest the combination *to arrive at the claimed invention.* Rather, one must make a leap to achieve the invention – by ignoring the express teachings of the screening procedure in Iris, the creation of diversity in specific episomal vectors in Stemmer, and the lack of purpose for introducing dominant negative alleles to create diverse organisms in Aronshtam. When the motivation to combine references does not come from the references themselves without having to resort to the Applicants teachings to supply the missing parts, a rejection for obviousness is not appropriate. Applicants respectfully request withdrawal of the rejection over Iris, Stemmer and Johnson in view of Aronshtam.

The Office Action also rejects claims 1, 2, 19, 27 and 38 under 35 U.S.C. §103(a) over Johnson in view of Iris and the combined teachings of LeClerc *et al.* (1996) *Science* 274:1208-1211 ("LeClerc") and either Drummond *et al.* (1995) *Science* 268:1909-1912 ("Drummond") or Moreland, *et al.* (1999) *Cancer Res.* 59:2102-2106 ("Moreland").

Johnson is cited for the proposition that antibiotic resistant bacteria may be identified by exposing the bacteria to a test antibiotic. Notably, the refernce is drawn to identifying bacteria that has innate resistance, and not generating antibiotic resistant bacteria. The method of Iris requires two populations of cells: one that displays the desired phenotype and one that does not. Like Johnson, Iris also fails to teach a method

of how to first obtain an antibiotic resistant organism. The hypothetical combination of Johnson and Iris would still be drawn to methods of identifying innate resistance by comparing two populations of organisms. This is totally different from the invention. The combined teachings of LeClerc, Drummond or Moreland are cited for teaching that bacteria may be made resistant to an antibiotic by introducing dominant negative alleles of a mismatch repair gene into the bacteria. The hypothetical combination may not be made without motivation to combine with a reasonable expectation of success. There is no motivation to combine the introduction of dominant negative alleles with the teachings or Johnson and Iris because the methods of Johnson and Iris are drawn to identification of innate resistance in cell populations, and neither contemplates first making cells resistant. Further, Applicants have included the feature of multiantibiotic resistance into the claims. None of the references, alone or in hypothetical combination address multiantibiotic resistance. Thus, there is no motivation to combine or reasonable expectation of success in achieving the instantly claimed invention.

Applicants respectfully request withdrawal of the rejection over this hypothetical combination of references.

The Office Action also rejects claims 1-3, 27 and 38 under 35 U.S.C. §103(a) over Iris in view of Stemmer and Johnson and further in view of Nicolaides *et al.* (1998) *Mol. Cell. Biol.* 18(3):1635-1641 (Nicolaides 2) or U.S. Patent No. 6,146,894 to Nicolaides *et al.* ("Nicolaides 3").

The Office Action admits that Iris in view of Stemmer and Johnson does not teach the inclusion of a dominant negative allele to make bacteria antibiotic resistant. Nicolaides 2 and Nicolaides 3 are relied upon to teach the inclusion of the dominant

negative allele of a mismatch repair gene. The hypothetical combination of references, however, does not teach or suggest making bacteria multiantibiotic resistant. The Applicants have incorporated the feature of multiantibiotic resistance from claim 26 (notably not rejected under this combination of references) into the main claims.

Thus, the claims are not obvious in view of the cited references. Applicants respectfully request withdrawal of the rejection over the hypothetical combination of references.

Applicants note that the Examiner addresses the alleged obviousness of claim 26 in paragraph 18 of the Office Action, and this argument is addressed below with reference to that combination of references.

The Office Action also rejects claims 1, 14-26 and 38 under 35 U.S.C. §103(a) over Iris in view of Stemmer and Johnson or over Johnson in view of Iris and the combined teachings of LeClerc and either Drummond or Moreland, and further in view of U.S. Patent No. 6,025,400 to Lin ("Lin"), U.S. Patent No. 6,043,220 to Chang *et al.* ("Chang"), U.S. Patent No. 6,410,056 to Stetterstrom *et al.* ("Stetterstrom"), and the Merck Index, 10th Edition, Merck & Co., Rahway, N.J., 1983, pp. 2036 and 5032-5033 ("Merck Index").

The Office Action bases the rejection with the combination of these references with the view that multiantibiotic resistance is embodied only in claim 26. The Applicants have amended the claims to include this feature in the main claims. Thus, the rejection under this section of the Office Action must take the comments for claim 26 into consideration for a complete rejection.

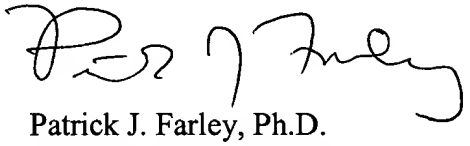
To this end, with reference to claim 26, the Office Action frankly admits that none of the cited references teaches a method for generating bacteria resistant to multiple antibiotics, but nonetheless concludes that such would be "obvious" since bacteria with multiantibiotic resistance are known. The Office Action suggests that the method of generating multiantibiotic resistance by introducing a dominant negative form of a mismatch repair gene into a microorganism is obvious merely because one would like to study multiantibiotic resistance. This is really just a statement that it would be "obvious to try" to generate such bacteria, but it does not address how one would go about generating the bacteria. It is axiomatic that "obvious to try" is not an acceptable grounds for a rejection under 35 U.S.C. §103. Thus, there is insufficient motivation to combine the references. Moreover, the Office Action presents no evidence of reasonable expectation of success that the hypothetical combination would be able to form a method that would generate bacteria that possessed multiantibiotic resistance.

Finally, the Office Action suggests that restabilizing the genome of hypermutable cells is "obvious" as one would desire to work with genetically stable organisms. However, none of the cited references teaches or suggests such a step. The suggestion for working with genetically stable organisms comes from the teachings of the Applicants and it is being used against the Applicants in the form of hindsight reconstruction, which is an improper basis for a rejection under 35 U.S.C. §103. Rejection under this basis should be withdrawn.

Conclusion

Applicants earnestly submit that the claims are in condition for allowance, which action is respectfully requested.

Respectfully submitted,



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